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BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Application Number: 09/926,661
Filing Date: February 28, 2002
Appellant(s): CHIBA, MASATOSHI

Bruce H. Bernstein
For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed 15 February 2007 appealing from the Office action mailed 16 February 2006.

(1) Real Party in Interest

A statement identifying by name the real party in interest is contained in the brief.

(2) Related Appeals and Interferences

The examiner is not aware of any related appeals, interferences, or judicial proceedings which will directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal.

(3) Status of Claims

The statement of the status of claims contained in the brief is correct.

(4) Status of Amendments After Final

The appellant's statement of the status of amendments after final rejection contained in the brief is correct.

(5) Summary of Claimed Subject Matter

The summary of claimed subject matter contained in the brief is correct.

(6) Grounds of Rejection to be Reviewed on Appeal

The appellant's statement of the grounds of rejection to be reviewed on appeal is correct.

(7) Claims Appendix

The copy of the appealed claims contained in the Appendix to the brief is correct.

(8) Evidence Relied Upon

Nakamura et al. EP 0456188A1. 13 November 1991

Tanaka WO 97/02832. 30 January 1997

Tanaka U.S. Patent Application Publication 2001/0051604. 13 December 2001.

(9) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

A. Claims 1, 3 – 4, 6 – 9, and 12 – 15 are rejected under 35 U.S.C. 102(b) as being anticipated by Nakamura (EP 0456188A1).

Briefly, independent claims 1 and 3 are drawn to lyophilized preparations comprising four elements: hepatocyte growth factor (hereinafter HGF), arginine, sodium chloride, and a buffering agent. The claims also recite the product-by-process limitation "which is prepared from an aqueous solution containing the hepatocyte growth factor at a concentration lower than 5 mg/ml." The claims differ in that claim 3 requires that the preparation be "capable of preparing an aqueous solution containing the hepatocyte growth factor at a concentration lower the 5 mg/ml by redissolution"; this is not recited in claim 1. While both claims 1 and 3 recite multiple stabilizing agents, the examiner required an election of species in the restriction requirement mail 28 June 2005. In the response to said requirement, filed 28 July 2005, appellant elected "arginine" for prosecution. Appellant confirmed this election in the brief filed 18 October 2006, on p. 8.

Nakamura teaches preparations comprising HGF. After a discussion of some of the properties and methods of preparing HGF, Nakamura discusses preparations, or compositions, comprising HGF. Specifically, beginning at column 9 line 45, Nakamura teaches that "[t]he therapeutic agents of the invention are generally formed into injections containing HGF *solely or combinedly* with carriers, etc. know per se. For example injections can be prepared by dissolving HGF in suitable buffers, followed by sterilization by filtration through a filter."

[emphasis added; note that here the prior art teaches two of the four required elements of the composition, namely HGF and a buffering agent.]

The next paragraph teaches the remaining elements of the composition. For the sake of brevity the paragraph will not be reproduced here, but note that the paragraph specifically states that the following items may be included: "arginine" (column 9, final line), "NaCl" (which is sodium chloride and is recited at column 10, line 3). Thus in these two paragraphs, Nakamura clearly teaches each of the four chemicals required to be in the composition. Nakamura also teaches the "surfactants such as Polysorbate 80" can be included (see column 10 lines 4 – 5); while this is not explicitly recited in either claims 1 or 3, it is on point to dependent claims 12 – 14. Finally, Nakamura teaches that the additives "*may be used alone or in combination.*" [emphasis added] Clearly Nakamura teaches that any of the elements listed can be added either individually or in a combination, i.e. all of them can be combined. The list of elements to be added is relatively small and by stating that they can be combined, Nakamura teaches the combination of elements now claimed.

Thus far it is clear that in the single passage, the prior art reference by Nakamura teaches each of the four chemicals required to be in the composition or preparation. Turning to the question of whether or not the reference teaches "[a] lyophilized preparation" as recited in independent claims 1 and 3, the very next paragraph of Nakamura (i.e. that beginning at column 10 line 7) addresses this point. Nakamura teaches that "[t]he liquid preparations are preferably stored by cryopreservation or after removal of water content by freeze-drying or vacuum drying." Note that "lyophilized" means that a liquid has been turned into a solid by freeze-drying the liquid under a vacuum. See for example appellant's specification, page 10 first complete paragraph. Clearly, Nakamura teaches that the liquid preparations are to be lyophilized, even though that exact term is not used.

The only limitation which is common to both independent claims 1 and 3 which has not yet been addressed herein is whether or not the reference anticipates the limitation "prepared from an aqueous solution containing the hepatocyte growth factor at a concentration lower than 5 mg/ml." First, it is important to note that this is a classic product-by-process limitation; it describes how the product can be made but does not distinguish the claimed product from the prior art. Product-by-process limitations are generally not given patentable weight. In *In re Thorpe*, the court held that

> "even though product-by-process claims are limited by and defined by the process, determination of patentability is based on the product itself. The

> patentability of a product does not depend on its method of production. If the product in the product-by-process claim is the same as or obvious from a product of the prior art, the claim is unpatentable even though the prior product was made by a different process." *In re Thorpe*, 777 F.2d 695, 698, 227 USPQ 964, 966 (Fed. Cir. 1985)

Although product-by-process limitations generally receive no patentable weight, in the instant situation the Nakamura reference addresses this limitation as well. See for example column 10 lines 17 – 19, which teaches that the doses to be administered to patients range from 0.01 mg to 100 mg; see also column 14 lines 25 – 34, which discusses a slightly different preparation comprising 1 mg of HGF in 100 ml of buffer prior to lyophilization (i.e. 0.01 mg/ml). Clearly, while the product-by-process limitation need not be explicitly taught by the prior art reference, Nakamura had conceived that preparing lyophilized compositions comprising HGF at a concentration of less than 5 mg/ml and had taught the public how to make this product.

Finally, the examiner turns to whether or not the reference by Nakamura teaches the limitation which appears in claim 3 and not claim 1, whether or not the preparation is "*capable of* preparing an aqueous solution containing the [HGF] at a concentration lower than 5 mg/ml by redissolution." [emphasis added] Note that the claim does not require that the lyophilized preparation be redissolved, or that any particular amount of the lyophilized preparation be present, or that any particular concentration be obtained. All that is required is that the preparation be capable of forming a solution comprising less than 5 mg/ml of HGF. Any amount of any lyophilized preparation is *capable of* forming a solution of any concentration, with the only reasonable boundary being the limit of solubility of the substance as an upper bound. If the artisan desires a solution of 5 mg/ml or less, he need only weigh out 5 mg of powder and add more than 1 ml of water. That will provide a solution of less than 5 mg/ml. Should the powder not completely dissolve, the artisan could add more water, thereby further *decreasing* the concentration and increasing the likelihood the powder will dissolve. For the reasons above, the reference by Nakamura anticipates both independent claims 1 and 3.

Claims 4, 6 – 9, and 12 – 15 all depend either directly or ultimately from claim 1. Claims 4 and 6 are limited to shorter lists of the stabilizing agent to be added, but each include arginine. The reasons why Nakamura anticipates claims to compositions comprising HGF and arginine are set forth above and for the sake of brevity are not repeated here. Claim 7 is limited to buffering agents which are phosphoric acid salts. Nakamura did not list all possible buffers when he listed the stabilizing agents. He did, however, teach the artisan to dissolve HGF "in

suitable buffers" (column 9 line 50). Elsewhere throughout the reference, including at Examples 1 and 2 (column 14 lines 25 - 45), Nakamura specifically teaches inclusion of phosphate buffer. Thus these later examples provide evidence that Nakamura considered phosphate buffer, which is a phosphoric acid salt, to be a member of the genus of suitable buffers. Claims 8 - 9 are drawn to inherent properties of the product before lyophilization and after dissolution. The reference is silent as to the actual pH of the composition taught on columns 9 - 10. However, a product and its properties are inseparable. Since the prior art reference teaches the composition of claim 1, and teaches that it is to be redissolved and administered to patients, it necessarily has the pH and osmotic pressures recited in claims 8 – 9. Claims 12 – 14 are drawn to compositions further comprising, in the most specific recitation, a polyoxyethylene ether surface active agent. Nakamura teaches that Polysobrate-80 is one of the agents which can be added to the composition (column 10 lines 4-5) and the specification clearly considers this to be a specific polyoxyethylene ether (see p. 9 final paragraph). It is noted again that Nakamura teaches that the agents listed in that paragraph can be used in *combination*. Claim 15 requires that the lyophilized product be prepared in a vial or an ampuole. Again, this is a product-by-process limitation which does not distinguish the product from the prior art. While Nakamura is silent, in this paragraph, as to whether or not the product is made in a vial, the container does not change the product contained therein.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

B. Claims 1 and 16 are rejected under 35 U.S.C. 102(b) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Nakamura.

The reasons why claim 1 is anticipated by Nakamura are set forth in the rejection under 35 USC 102(b) above. Briefly, the reference by Nakamura teaches the same composition set forth in claim 1. The reference is silent as to whether or not the stabilizing agent arginine is present "in an amount sufficient to prevent HGF aggregate formation" as recited in claim 16.

However, rejections under 102/103 in the alternative are proper when the prior art teaches a composition that appears to be identical but is silent as to an inherent property; see MPEP § 2112(III). Here, the prior art teaches the composition comprising HGF and arginine but is silent as to whether the amount of arginine included is sufficient to prevent aggregate formation. It is noted that appellant has not supplied any evidence to distinguish the invention of claim 16 from that of either claim 1 or the prior art reference by Nakamura.

C. Claims 1, 3, 4, and 6 – 16 are rejected under 35 U.S.C. 103(a) as being unpatentable over Nakamura (European Patent Application 0456188A1), in view of Tanaka et al. (WO 97/02832, published 30 January 1997), as evidenced by Tanaka et al. (U.S. Patent Application Publication 2001/0051604, published 13 December 2001, cited by applicant on IDS filed 27 February 2004). The U.S. Patent Application Publication 2001/0051604 is the national stage entry of the PCT application that was published as WO 97/02832. Since 35 USC § 372(b)(3) requires that the application be submitted in English upon entry to the national stage, the '604 publication is a proper translation of the earlier Japanese document. The page and paragraph numbers cited herein are from the '604 publication but the same information was disclosed in Japanese in the earlier WIPO publication.

The reasons why claims 1, 3, 4, 6 – 9 and 12 – 16 are anticipated by, or in the alternative obvious over, Nakamura are set forth in the rejection under 35 USC § 102(b) above. Briefly, Nakamura teaches lyophilized preparations comprising HGF and stabilizers as claimed by applicant. However, Nakamura does not teach pH of the solution before lyophilization in the range of 5 to 6.5.

Tanaka teaches preparation of lyophilized HGF wherein the pH of the solution before lyophilization is between 5.0 and 6.5, and further comprising stabilizing agents including amino acids (see page 2, paragraph 0017), and buffering agents to keep the pH in the desired range. Specifically, Tanaka teaches buffers comprising citrate, which have a pH between 5.0 to 6.0 (see page 2, paragraph 0018). Tanaka teaches that keeping the pH between 5.0 and 6.0 is advantageous, as HGF shows increased solubility at this pH. Thus the teachings of Tanaka are on point to claims 10 and 11. Tanaka also teaches that lyophilization according to their disclosed method is sufficient to prevent aggregate formation (see page 1, paragraph 0006), which is relevant to claim 16. However Tanaka does not teach compositions comprising arginine recited in claims 1, 3, 4, and 6.

It would have been prima facie obvious to one of ordinary skill in the art to make the lyophilized preparation of Nakamura using the buffer with pH 5.0 – 6.5 as taught by Tanaka, with a reasonable expectation of success. Tanaka teaches that the lower pH range is advantageous, as HGF is more soluble in the more acidic environment. Therefore one of ordinary skill in the art would be able to make the preparation faster, as it would take less time for the HGF to dissolve. It would be reasonable to expect success, as both references are drawn to the same subject matter, namely preparation of lyophilized HGF.

(10) Response to Argument

A. Appellant argues, that the reference by Nakamura fails to anticipate the claimed invention because it does not "clearly and unequivocally disclose all of the elements of Appellant's claimed subject matter *with sufficient specificity*." (Appeal Brief, sentence spanning pp. 10 – 11, emphasis in original) Appellant argues that there is no motivation to pick and choose from the several elements listed in Nakamura to arrive at the invention now claimed. Appellant argues "that the rejection improperly utilizes Appellant's disclosure as a guide to pick and choose from Nakamura's broad disclosure". Appellant's arguments have been fully considered but they should not be found persuasive.

The reason why each and every limitation of independent claims 1 and 3 has been met by Nakamura is set forth in section (9)(A) above. The claims are drawn to lyophilized preparations comprising four chemicals. Nakamura teaches the compositions and teaches freeze-drying, or lyophilizing, them. Appellant argues that the rejection of record improperly picks and chooses from among the elements listed in Nakamura's broad disclosure. This is not the case. First, it is important to note that the claimed elements (HGF, arginine, sodium chloride, and a buffer) are all named in the section spanning columns 9 – 10 of Nakamura. Claims to a species are anticipated when the prior art names that species, no matter how many other species might also be named in the reference; see MPEP § 2131.02. Here, each of the elements listed in the independent claims are explicitly listed in Nakamura, columns 9 – 10. Second, Nakamura teaches that the elements listed can "be used alone or in combination" (emphasis added; see column 10 line 6, which follows the list of compounds that can be added; see also column 9 lines 45 – 50, immediately before this list, which also indicates that the elements can be added solely or in combination). Thus Nakamura clearly told the public that his invention took several forms, was not limited to specific examples, and could include the

elements listed in combinations. Third, independent claims 1 and 3 both use open claim language. Both begin with the phrase "[a] lyophilized preparation *comprising*" [emphasis added] certain elements. Use of the word "comprising" allows for the inclusion of additional elements not recited in the claim. Nakamura teaches all the elements recited in the claims, as well as several which do not appear, and says that they may be combined. Therefore, the reference fairly anticipates the invention now claimed.

Applicant also cites the Board's decisions in *Ex parte Bobstein* and *In re Arkley* in support of the argument that picking and choosing among elements of a reference does not constitute anticipation. Of course Appellant is aware that *Bobstein* was not published and does not constitute binding precedent on the board (see cover page of the *Bobstein* decision). Nonetheless, the decision in Bobstein is not in fact on point to the instant situation. In *Bobstein*, the Board found that the composition claimed was not anticipated by the prior art reference, as the artisan would have to pick and choose from among several pigments to arrive at Bobstein's invention. Here, no such picking and choosing is necessary for the artisan. The artisan would only have to follow the directions set forth in Nakamura, columns 9 – 10, which teach that the elements can be added individually or can be combined. If all elements are combined, then the composition will be one comprising the elements now claimed, as well as several others. With respect to *Arkley*, cited in *Ex parte Bobstein*, the issue is much the same. In *Arkley*, the court ruled that the identical compound must be disclosed in order for the invention to be anticipated under 35 USC § 102, and emphasized that no picking or choosing from among the various components listed can be required by the skilled artisan. In the instant case, the claims are drawn to lyophilized compositions *comprising* four elements: HGF, a buffer, sodium chloride, and arginine and lyophilized compositions *comprising* those same four elements are taught in the prior art. As set forth above, the reference by Nakamura discloses compositions comprising a buffer, sodium chloride, and arginine, among others, and teaches that they may be added to the HGF-containing compositions, singly or combinedly. Every element of the composition now claimed is disclosed, and the prior art teaches combining them. No picking, choosing, or selecting is required on the part of the artisan.

On p. 12 of the brief, appellant argues that Nakamura does not describe arginine as a stabilizing agent. Whether or not it is explicitly described as having "stabilizing" properties is immaterial. The compositions comprising arginine, now claimed, are identically described in the prior art and old products do not become patentable upon discovery of a novel property.

With respect to claims 4, 6 – 7, and 12 – 15, the reasons why Nakamura anticipates each of these claims is set forth in section 9(A) above. The identical compositions are described by Nakamura in their entirety and thus the claims are anticipated. With respect to claim 8, whether or not the composition "has a pH and an osmotic pressure ratio desirable as an injection" prior to lyophilization is a question of fact. The pH and osmotic pressure are inherent properties of the composition. Since the identically-disclosed composition is described in Nakamura, it must have the same properties since a composition and its properties are inseparable. No particular pH or osmotic pressure values are recited in claim 8, and no evidence has been presented by appellant to distinguish the invention of claim 8 from that of claim 1 or from Nakamura. Similarly, claim 9 requires that the composition have these properties after redissolution. Whether or not it has these properties depends on the components of the composition. Since the prior art teaches the composition, it must have these properties. Therefore, the rejection of claims 1, 3, 4, 6 – 9 and 12 – 15 under 35 USC 102(b) should be maintained.

B. Appellant argues, on pp. 17 – 19 of the brief, that the rejection of claims 1 and 16 as anticipated by, or in the alternative obvious over, Nakamura is improper. With respect to claim 1, the reasons why it is anticipated by Nakamura are discussed above and will not be reiterated here. Claim 16 depends from claim 1 and requires "the stabilizing agent in an amount sufficient to prevent HGF aggregate formation" either during lyophilization or subsequent storage.

The examiner has conceded that the reference by Nakamura does not teach the exact amounts of arginine added, and does not report whether adding arginine decreases aggregate formation. However, the prior art reference need not actually disclose all properties of a composition for that composition to be anticipated. See MPEP § 2112. As the prior art discloses the composition now claimed in claim 1, it is reasonable that the composition actually has the property recited in claim 16.

With respect to whether the rejection should be one under § 102 or § 103, the examiner has used the guidance set forth in MPEP § 2112(III) to determine that the rejection can be made in the alternative. This section states, in part,

> Where applicant claims a composition in terms of a function, property or characteristic and the composition of the prior art is the same as that of the claim but the function is not explicitly disclosed by the reference, the examiner may make a rejection under both 35 U.S.C. 102 and 103, expressed as a 102/103 rejection. "There is nothing inconsistent in concurrent rejections for obviousness

> under 35 U.S.C. 103 and for anticipation under 35 U.S.C. 102." In re Best, 562 F.2d 1252, 1255 n.4, 195 USPQ 430, 433 n.4 (CCPA 1977).

That is exactly the situation here. The prior art discloses a composition identical to that now claimed in claims 1 and 3. Claim 16 further defines the composition "in terms of a function, property or characteristic ... but the function is not explicitly disclosed by the reference". The examiner also noted that after setting forth a *prima facie* case of inherency, the burden is on applicant (now appellant) to distinguish the claimed invention from the prior art, as set forth in MPEP § 2112(V). See Final Rejection mailed 16 February 2006, page 5 paragraph 12. Appellant's failure to distinguish the invention now claimed from that disclosed in the prior art led the examiner to properly maintain the rejection. Thus claims 1 and 16 were properly rejected under 35 USC 102(b) as anticipated by, or in the alternative under 35 USC 103(a) as obvious over, Nakamura and the rejection should be maintained.

C. Appellant argues, on pp. 20 – 26, that the rejection of claims 1, 3, 4, and 6 – 16 as obvious over Nakamura in view of Tanaka (WO 97/02832) is improper and should be withdrawn. The examiner notes that claims 1, 3, 4, 6 – 9, and 12 – 16 have been discussed in considerable detail in the section under anticipation above. These claims are included in the instant rejection solely for the sake of completeness; no motivation for picking and choosing any particular elements is required as the prior art reference by Nakamura teaches compositions *comprising* every element of those claims. The only claims yet to be discussed are those which are not actually anticipated by Nakamura, specifically claims 10 – 11.

Claims 10 – 11 both depend from claim 1. Claim 10 requires that the composition has a pH in the range of 5 to 6.5 prior to lyophilization. Nakamura teaches compositions, but does not explicitly teach modifying the pH to the 5 – 6.5 range. As set forth above in section (9)(C), Tanaka teaches that when preparing slightly different compositions (which include HGF and are to be lyophilized but do not include arginine), modifying the pH so that it is between 5.0 – 6.5 is advantageous, as it increases the solubility of HGF in the liquid. This provides the motivation to the artisan of ordinary skill to modify the invention set forth in Nakamura. Increasing the solubility would be advantageous, because when solubility increases more of a compound will dissolve. This would allow the artisan to prepare the composition faster, since it would not take as much time for the HGF to dissolve.

Appellant argues, on p. 20 of the brief, that Tanaka teaches away from the invention because the claims require the lyophilized preparation to be prepared from a liquid with a concentration of less than 5 mg/ml of HGF. Appellant argues that "Tanaka et al. clearly suggests a higher concentration of HGF than 5 mg/ml." (brief, p. 20) Appellant's arguments have been fully considered but they are not persuasive. There are several reasons one of ordinary skill would be motivated to increase solubility. One reason might be to prepare a more concentrated solution, as appellant states. However, Tanaka's disclosure is certainly not limited to highly concentrated solutions. Another motivation to increase solubility, as stated previously, is to allow for more rapid preparation of the composition. A solute that is highly soluble in a solvent will dissolve more rapidly than one weakly soluble in the same solvent. Tanaka teaches how to increase the solubility of HGF, i.e. by lowering the pH of the solvent so that it is between 5 and 6, and even calls this the "preferred" range. The artisan of ordinary skill would clearly be motivated to follow the explicit guidance in Tanaka, as this would allow the artisan to make the composition faster. Therefore, it would have been *prima facie* obvious to one of ordinary skill in the art to modify Nakamura's invention and arrive at the composition of claim 10.

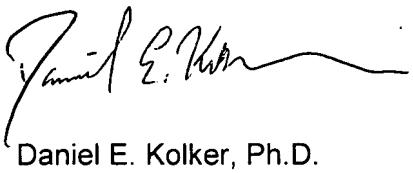
With respect to claim 11, once the aqueous composition is lyophilized, it is a dry powder. Nakamura teaches that lyophilized compositions can be reconstituted by adding water (see for example column 14 lines 25 – 34). Since the composition has all the salts, buffers, and other components it had before lyophilization, adding water will restore a solution identical to that present before lyophilization. Thus reconstituting a lyophilized preparation that had pH 5-6.5 prior to lyophilzation with water will result in a composition with the same pH after redissolution. Therefore, since claims 1 and 10 are obvious over Nakamura in view of Tanaka, and Nakamura teaches reconstituting lyophilized preparations with water, claim 11 is also obvious over Nakamura in view of Tanaka. Therefore, the rejection of claims 1, 3, 4, and 6 – 16 as obvious over Nakamura in view of Tanaka should be maintained.

(11) Related Proceeding(s) Appendix

No decision rendered by a court or the Board is identified by the examiner in the Related Appeals and Interferences section of this examiner's answer.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,



Daniel E. Kolker, Ph.D.

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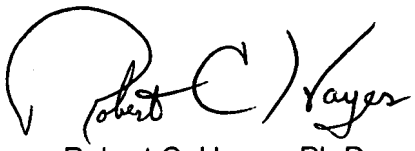

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